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Synthesis of Novel Medicinally Important Aromatic and/or Heterocyclic Compounds by Applying Various Methods and its Pharmacological Evaluation

Research Proposal submitted
In partial fulfilment of registration to

Ph.D. Programme

In the subject

Chemistry
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Submitted by

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THESIS TITLE

"Synthesis of Novel Medicinally Important Aromatic and/or Heterocyclic Compounds by Applying Various Methods and its Pharmacological Evaluation."

1.Introduction :

Chemical substances have "Toxicity" as a property and its exposer mainly depend based on the way it is used. Hence, chemicals continuously deal with the toxic, hazardous and flammable organic solvents. Organic solvents used in most of the synthesis processes in chemical industries evaporate into the atmosphere with adverse effects on the environment and directly/ indirectly on all living organisms. It is amongst the major causes for water, land and air pollution. Generally, such organic solvents are expensive challenging to reuse or recycle and not cost efficient to dispose. Since many decades a lot of research & developments is going on to overcomes this profound issue.

Green chemistry is an eco-friendly and an efficient method for the synthesis of medicinally potent molecules. Green chemistry uses efficient solvents and catalysts for the synthesis of drug molecules. This method reduces the environmental pollution and prevents the toxic effect of chemicals on human and animals. It involves different methods useful in the field of the organic chemistry and medicinal chemistry. One of the new areas of study is "Ionic Liquids" are free flowing liquids at room temperature known as room temperature ionic liquids (RTILs). Ionic liquids have potential properties to increase chemical reactivity and to enhances the more efficient process. Ionic liquids are non-flammable & non-volatile due to their low vapor pressure.

Other well-known green and fast methods for synthesis of organic compounds are use of "Microwave Irradiation" and "Ultrasound Sonication". These are choice of fast synthesis of many medicinal, pharmaceutical and academic laboratories. Microwave not only significantly shorten reaction times and improve reaction yields and selectivity, but are also more environment friendly than traditional conventional methods. The microwave irradiation creates superheating effect directly inside the solvent. The steady growth of interest in the synthesis of heterocyclic compounds is connected with their importance in the biological.

Here, we are proposing the synthesis of different ionic liquids based on different heterocycles like imidazole, pyridine, thiazole, alkyl phosphine compounds by changing their anions. Synthesized compounds will be characterized by 1H-NMR, MS analysis. Newly synthesized

ionic liquids will be used as green media for synthesis of biologically active compounds like quinoxalines, imidazole, benzimidazoles, azetidinones, nitrogen etc.We are proposing the synthesis of above compounds by their comparison of synthesis of existing methods with the novel media i.e., Microwave & ionic liquids separately, also in combination.

2. Molecules Introduction:

The piperidine structural design is found as a constituent of numerous alkaloids, several of which possess significant pharmacological properties.[1] There is unabated interest in the study of 4-aryl-l,4-dihydropyridines (DHPs) as a consequence of their pharmacological activity as the most important class of calcium channels modulators.[2-4] Since the earlier crystallographic studies[5] directed to the definition of a structure-activity relationship for these types of compounds, a big effort has been devoted to the synthesis of differently substituted DHPs[6]. In addition to the chemical modification carried out on the periphery of the parent nifedipine. Many naturally occurring and synthetic compounds containing the 2-pyridone scaffold possess interesting pharmacological properties as they are identified as specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV- 1). Milrinone[7-8], Amrinone[9] and their analogues are cardiotonic agents for the treatment of heart failure. Some 2-pyridones are also reported to possess antitumor, antibacterial, antimicrobial, antiviral, antifungal, antihypertensive and other biological

3. Purpose of proposed research work :

Purpose of this research work to out find wide range of pharmacologically active drug candidates for the betterment of human kinds using easily available raw material (chemical), cheap raw materials in environmental benign reaction conditions/media.

4. Survey or review of literature :

- A number of synthetic methods for the preparation of pyridones have been reported in the literature due to its broad-spectrum biological activities and its skeleton. In this section we have reviewed some of the important synthetic methods for the preparation of 3,4-dihydro-2-pyridones which have appeared in the literature recently.
- Svetlik et al. reported the synthesis of 4-substituted aryl-3,4-dihydropyridones, from condensation of aromatic aldehyde, Meldrum's acid, methyl acetoacetate, ammonium acetate and acetic acid in refluxing methanol which afforded desired product in very poor yield even after long reaction period.

- Seaone et al. reported very similar method to that of Svetlik's approach for the synthesis of 3,4- dihydropyridone, wherein a mixture of aromatic aldehyde, Meldrum's acid, methyl acetoacetate and ammonium acetate was heated in acetic acid at 110oC which afforded desired product in better yield as compared to the earlier method (Svetilk's approach).
- 4-Aryl substituted-5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones have been synthesized in one-pot condensation from aromatic aldehyde, Meldrum's acid, methyl acetoacetate and ammonium acetate under solvent free conditions using microwave irradiation as alternative to conventional heating. This rapid method produced pure products in excellent yields (81–91%) compared to conventional heating (17–28%) under the identical condition.
- Paravidino reported synthesis of functionalized 3-isocyano-3,4-dihydro-2-pyridones 124 from phosphonate, nitriles, aldehydes. Reaction of phosphonate, nitrile and aldehyde and n-BuLi in THF at - 78^{o}C to rt affords the 1-azadienes which on further cycloaddition with methyl-2-isocyano-2- phenylacetate in THF gave 3-isocyano-3,4-dihydro-2-pyridones in good yield.
- Feng-Ping et al. synthesized task specific hydroxyl functionalized ionic liquid 1- (2-hydroxyethyl)-3- methylimidazolium tetrafluoroborate via microwave irradiation using methylimidazolium, chlorohydrin and sodium tetrafluoroborate which was used for the synthesis of 3,4-dihydropyridones. Methyl acetoacetate on treatment with gave intermediate which on condensation with Meldrum acid, ammonium acetate and aromatic aldehyde afforded 3,4-dihydropyridones in good yields 80-90% after cleavage by treatment with strong base in methanol.
- Several other methods of significance which involves the synthesis of 3,4-dihydro-2-pyridones can be found in the literature.

5. Research gap(s) :

The general and common methods towards 3,4-dihydro-2-pyridones require multistep synthesis[10] usually via a combination of three steps: (1) a condensation, (2) a conjugate addition, and (3) an elimination. Most of this multi-step synthesis and suffer from other drawbacks such as use of acidic or and moisture sensitive catalysts, low yields, cumbersome isolation procedure, long reaction time period and specific starting material (synthesized from several steps).

6. Importance of the study:

A lot of research work is going on all over the world to investigate organic compounds which will act as effective medicines as anti-HIV, anti-Cancer and anti-tuberculostatic drug Antibacterial. National Institutes of Health, National Cancer Institute, Bethesda, Maryland, USA showed keen interest in evaluation of compounds, identified in our earlier research publications for anti-HIV and anticancer screening. It is surmised that some newly synthesized compounds mentioned in our proposal would exhibit properties required for effective drugs. Synthesis and screening of newly synthesized compounds would lead to the formation of pharmacological important compounds as a good antibacterial.

7. International status:

Prof. Svetlik et al.[11] reported the synthesis of 4-substituted aryl-3,4-dihydropyridones condensation of substituted aromatic aldehydes, methyl acetoacetate, ammonium acetate and acetic acid in refluxing methanol which afforded desired product in very poor yield even after long reaction period

Prof. Seaone et al. [12] reported the synthesis of 3,4-dihydropyridone wherein a mixture of aldehydes, methyl acetoacetate and ammonium acetate was heated in acetic acid at 110 °C which afforded desired product in low yield

8.National status:

Prof. A.Yadav (from IISER, Bhopal) et. al.[13] in 2015 synthesized substituted dihydropyridin-2(1H)-ones, pyridin-2(1H)-ones, and thiopyridin-2(1H)-ones using KOtBu in acetonitrile, however it was suffered from expensive and moisture sensitive reagents, low yield, functional group tolerance.

Prof. A. Mukherjee et. al.[14] in 2021 synthesized substituted dihydropyridin-2(1H)-ones using expensive and less available chiral catalyst in harsh reaction conditions, environmentally unfriendly solvents such as benzene

9. Regional status :

Dr. Akkattu T. Biju[15] from NCL-Pune (Maharashtra) reported NHC-organocatalyzed annulation of 2-bromoenals with readily available 1,3-dicarbonyl compounds or enamines proceed ing via the chiral α,β–unsaturated acylazolium intermediates. The reaction furnished an enantioselective synthesis of dihydropyran ones and dihydropyridinones, which are suffered with multi step synthesis, expensive reagents/catalyst, anhydrous/special reaction conditions, long reaction time, cumbersome isolation procedure and low reaction yield.

10. Objectives :

- Since 3,4-dihydro-2-pyridones serve as valuable building blocks in the construction of piperidines, perhydroquinolones, indolizidines, quinolizidines and other alkaloid ring systems and have a wide range of biological and pharmacological activities.
- The general and common methods towards 3,4-dihydro-2-pyridones require multistep synthesis, usually via a combination of three steps: (1) a condensation, (2) a conjugate addition, and (3) an elimination.
- Over the past decade, room temperature ionic liquids (RTILs) have emerged as a new class of stable and inert solvents.
- Indeed, this family of ionic moieties presents several interesting properties compared to classical molecular solvents.
- They exhibit high thermal stability, high polarity due to their ionic nature and a great ability to solubilize polar and non-polar organic compounds.
- Moreover, their immiscibility with molecular solvents and their very low vapor pressure makes them very good solvents for both extraction and recyclability.
- The use of ionic liquids as solvents for chemical transformations is also of a topical interest in academia and industry according to the twelve principles ruling Green Chemistry.
- Literature survey for proposed research work.
- The title compounds shall also be synthesized under Microwave irradiation using various ionic liquids.
- Results shall be compared by conventional method and Microwave irradiation technique.
- Structure of synthesized compound shall be elucidated by spectrochemical analysis (UV, IR, LCMS, NMR etc.)
- Synthesized compounds shall be screened for their biological activities viz antibacterial, antifungal activity etc. and results shall compare with standard drugs.

11. Hypothesis :

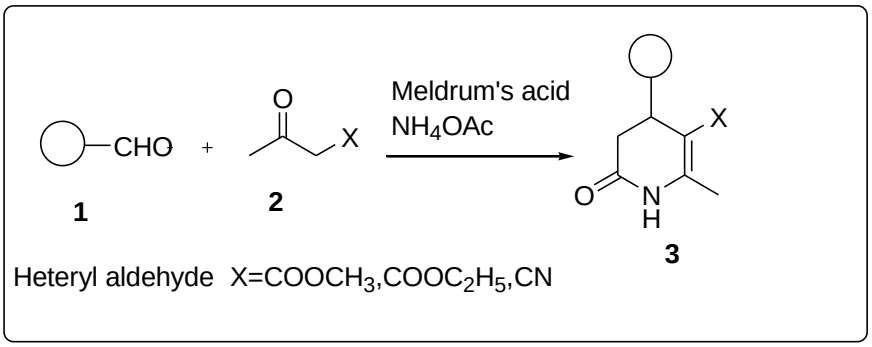
We are hypothesizing the inherent properties of ionic liquids such as acidity, solubility (due to ionic bonding) will lead to good yield, less reaction time and wide variety of functional group tolerance on aldehyde, beta-keto esters.

12. Research Methodology:

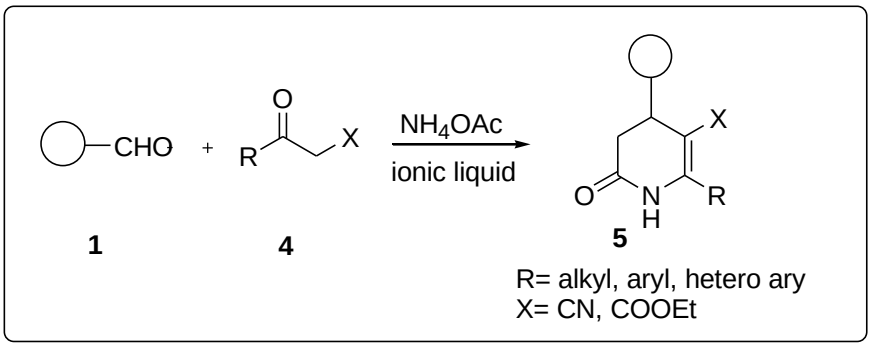
- By known and novel three component system synthesis of different 3,4-dihydro-2-pyridones.
- Pharmacological evaluation of above synthesized compounds.

13. Proposed Reaction Scheme:

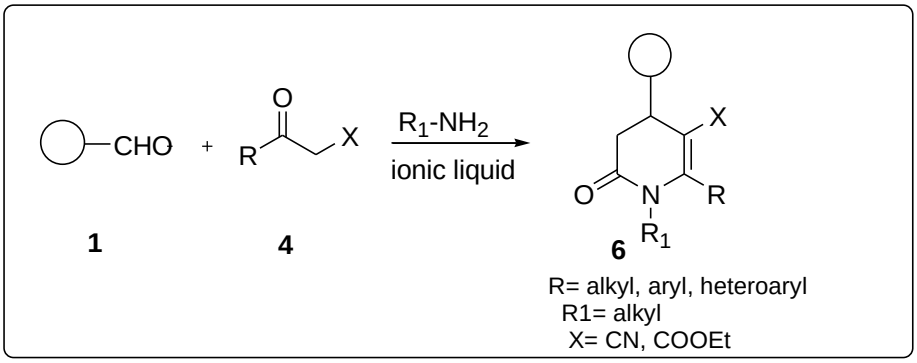
Scheme 1**: Synthesis of 4-heteroaryl substituted 5-cyano or 5-alkoxycarbonyl-6-methyl-3,4- dihydropyidones**



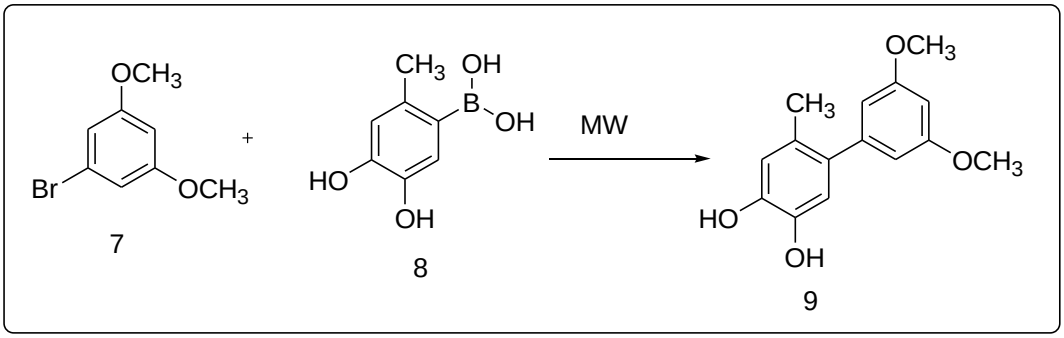
Scheme 2: **Synthesis of 4-heteroaryl substituted 5-cyano or 5-alkoxycarbonyl-6-methyl-3,4-dihydropyidones using ionic liquids**



Scheme 3: **Synthesis of 4-substtuited-1-alkyl-6-oxo-2-sustituited-1,4,5,6-tetrahydro-pyridine-3-carbonitrile or alkoxy carbonyl**



Scheme 4: **Synthesis of Decarboxyaltenusin**



14. Limitation(s) of the work:

Cost effect and commercial availabilities of reagent.

15. Expected outcome:

To generate numerous pharmacologically active target molecule with easily available, cheap, environmental friendly conditions in short period of span.

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16. Year wise plan of work and targets:

Year	Quarters (Periods of three months)	Milestones
Year I	1 st Quarter	Reference Work
	2nd Quarter	Topic first literature survey
	3rd Quarter	Topic first Experimental Work and characterization
	4th Quarter	Topic second literature survey
YearII	1 st Quarter	Topic second Experimental Work and characterization
	2nd Quarter	Topic third literature survey
	3rd Quarter	Topic third Experimental Work and Characterization
Year III	4th Quarter	Topic Fourth literature survey
	1 st Quarter	Topic Fourth Experimental Work and characterization
	2nd Quarter	Topic Fifth literature survey and Experimental Work and characterization
	3rd Quarter	Topic sixth Biological evaluation
	4th Quarter	Writing and typing of the research work and submission of the research work

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